

# Screening for pre-eclampsia and fetal growth restriction in twin pregnancies at 23 weeks of gestation by transvaginal uterine artery Doppler

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**KEYWORDS:** Doppler ultrasonography, Fetal growth restriction, Pre-eclampsia, Screening, Transvaginal, Twin pregnancy, Uterine arteries

## ABSTRACT

**Objective** To assess the value of transvaginal uterine artery Doppler at 23 weeks of gestation in predicting the development of adverse perinatal outcomes in twin pregnancies.

**Patients and methods** Women with twin pregnancies attending for routine ultrasound examination at 23 weeks in any one of seven hospitals underwent Doppler assessment of the uterine arteries. The right and left uterine arteries were identified using color flow mapping and velocity waveforms were obtained using pulsed Doppler. The mean pulsatility index (PI) of the two arteries was determined and the presence of uterine artery notching noted. Results were compared between monochorionic and dichorionic twins, and with our previously reported data from singleton pregnancies. Screening characteristics in the prediction of pre-eclampsia, fetal growth restriction (FGR), placental abruption, fetal death and early preterm delivery were calculated.

**Results** Uterine artery Doppler at 22–24 weeks of gestation was performed in 360 twin pregnancies, including 324 dichorionic and 36 monochorionic diamniotic twins. Complete outcome data were available in 351 (97.5%). The mean uterine artery PI did not change significantly with gestation and there was no significant difference in mean PI between the dichorionic and monochorionic groups. However, the mean PI was significantly lower in twin pregnancies than in singletons. The pregnancy was complicated by pre-eclampsia in 6.0% of cases, FGR below the 5th centile of both twins in 8.8%, abruption in 0.9%, intrauterine fetal death in 1.7% and early preterm delivery at less than 32 completed weeks of gestation in 5.7% of cases. The respective sensitivities of uterine artery mean PI above the 95th centile for these complications were 33.3%, 9.7%, 66.6%, 33.3% and 18.6%.

**Conclusions** In twin pregnancies PI in the uterine arteries is lower than that in singleton pregnancies, but there is no

significant difference between dichorionic and monochorionic twins. Doppler assessment of the uterine arteries at 23 weeks identifies a large proportion of twin pregnancies destined to develop adverse outcomes related to uteroplacental insufficiency.

## INTRODUCTION

In twin pregnancies, compared with singletons, there is a higher incidence of pre-eclampsia and higher perinatal mortality, mainly due to prematurity-related complications and fetal growth restriction (FGR)<sup>1–5</sup>. In singletons, pre-eclampsia and FGR are thought to be the consequence of failure of trophoblastic invasion of the maternal spiral arteries resulting in a reduction in placental perfusion<sup>6–8</sup> and it is thought that a similar pathogenesis may occur in twin pregnancies<sup>1</sup>. Doppler ultrasound is a reliable and noninvasive method of assessing the uteroplacental circulation<sup>9,10</sup>. In singletons, increased impedance to flow in the uterine artery carries a six-fold increase in the likelihood of pre-eclampsia, while normal impedance is associated with a reduction by a factor of about two<sup>11</sup>. However, there have been limited studies on the use of Doppler ultrasound for the prediction of uteroplacental complications in twin pregnancies.

The aims of this study were to compare pulsatility index (PI) in the uterine arteries in singleton pregnancies with monochorionic and dichorionic twin pregnancies and to assess the value of transvaginal uterine artery Doppler velocimetry at 23 weeks in predicting the development of adverse perinatal outcomes in twin pregnancies.

## MATERIALS AND METHODS

In this screening study, which was carried out between January 2000 and April 2002, transvaginal Doppler assessment of the uterine arteries was performed in twin pregnancies at 22–24 weeks of gestation for the prediction of subsequent

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development of pre-eclampsia, FGR, placental abruption, intrauterine death and early preterm delivery.

Sonographers performing the Doppler studies had received the Certificate of Competence in Doppler from The Fetal Medicine Foundation ([www.fetalmedicine.com](http://www.fetalmedicine.com)) and quality control of screening was performed on a regular basis by the trial coordinators. The participating hospitals were Basildon Hospital, Basildon, Greenwich Hospital, London, Harold Wood Hospital, Essex, King George Hospital, Essex, King's College Hospital, London, Queen Mary's Hospital, Sidcup and University Hospital, Lewisham. The study was approved by the South Thames Multi Centre Research Ethics Committee as well as the local ethics committees of individual hospitals, and written informed consent was obtained from all women.

Women were recruited to the study at the routine second-trimester ultrasound scan at 22–24 weeks for measurement of fetal growth and examination of fetal anatomy. All women with two live fetuses, no obvious major fetal abnormality and no evidence of twin-to-twin transfusion syndrome were offered the option of a transvaginal scan to measure both cervical length, as a method of screening for preterm delivery, and uterine artery Doppler studies to screen for pre-eclampsia and FGR.

The transvaginal scan was performed as previously described<sup>11</sup>. After identification of the uterine artery using color Doppler, pulsed wave Doppler was used to obtain three similar consecutive waveforms, the presence or absence of an early diastolic notch was noted and the PI was measured. The same was repeated for the contralateral uterine artery and the mean PI of the two vessels was calculated.

Demographic characteristics and Doppler findings were recorded in a computer database at the time of the ultrasound examination in each participating center. Subsequently, routine antenatal care was carried out regardless of the uterine artery Doppler findings.

All cases had previously undergone an ultrasound scan at 11–14 weeks of gestation with the aims of determining gestational age and chorionicity, diagnosing major fetal defects and measuring nuchal translucency thickness as part of screening for chromosomal abnormalities. Chorionicity was determined as previously described<sup>12</sup> according to the presence or absence of an extension of placental tissue into the base of the intertwin membrane visualized sonographically as the lambda sign in dichorionic twin pregnancies, and the T sign in monozygotic twins. Gestational age was calculated on the basis of the last menstrual period (LMP). Pregnancies were dated by measurement of the crown–rump length (CRL) of the larger twin if the discrepancy was more than 7 days. Dating by CRL was also carried out in cases where the LMP was unknown or uncertain and in those with an irregular cycle or recent use of the oral contraceptive pill or pregnancy less than three cycles prior to conception.

Data on pregnancy outcome were obtained from examination of individual patient notes and labor ward records. Outcome measures were pre-eclampsia, FGR, placental abruption, intrauterine death and severe preterm delivery. Pre-eclampsia was defined according to the guidelines of the International Society for the Study of Hypertension in

Pregnancy. This requires two recordings of diastolic blood pressure of  $\geq 90$  mmHg at least 4 h apart in previously normotensive women, and proteinuria of 300 mg or more in 24 h, or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-h collection is available<sup>13</sup>. FGR was defined as birth weight less than the 5th and 3rd centiles for gestation of singleton pregnancies<sup>14</sup>. Placental abruption was defined as antepartum hemorrhage with evidence of retroplacental clot confirmed at delivery. Intrauterine death was defined as stillbirth after 24 weeks of gestation. Early preterm delivery was defined as delivery prior to 32 completed weeks of gestation.

### Statistical analysis

Categorical variables were analyzed using chi square or Fisher's exact test, while continuous variables were compared using unpaired *t*-test, Kruskal–Wallis, Mann–Whitney *U*-test and linear regression where appropriate. Two-sided significance tests are reported and the alpha error was set to 0.05. Normal ranges for PI were constructed and compared between dichorionic and monozygotic twins as well as to 7851 singleton pregnancies screened using the same methodology<sup>11</sup>. The sensitivity, false positive rate, positive predictive value, negative predictive value and likelihood ratio with 95% confidence intervals for a cut-off mean PI above the 95th centile and presence of bilateral uterine artery notching were calculated. Statistical analysis was performed using MS Excel 2000 and Arcus Quickstat Biomedical, Version 1.2.

## RESULTS

Doppler examination of the uterine arteries was carried out in 360 consecutive twin pregnancies, including 324 dichorionic and 36 monozygotic diamniotic. Complete outcome data were available in 351 (97.5%) of the total group (316 (97.5%) of the dichorionic group and 35 (97.2%) of the monozygotic group), and this constituted the study population. The median gestation at screening was 23 weeks (range 22–24 weeks). The demographic and screening characteristics of the study population are shown in Table 1.

Adverse pregnancy outcomes are shown in Table 2. Pre-eclampsia occurred in 21 (6.0%) cases. Pregnancies where both fetuses were affected with FGR below the 5th centile occurred in 31 (8.8%) of cases, and in 83 (23.6%) cases there was FGR of one, but not the other fetus. The respective numbers for FGR below the 3rd centile were 22 (6.3%) and 63 (17.9%). There were three cases of abruption, six of intrauterine death and 43 (12.3%) preterm deliveries before 32 completed weeks. Of the 43 early preterm deliveries, 32 were spontaneous (of which five (15.6%) had a high PI) and 11 were iatrogenic (of which three (27.3%) had a high PI).

The mean PI was significantly lower in both twin groups when compared with singletons (Kruskal–Wallis test for the three groups  $T = 66.2$ ,  $P < 0.0001$ ; dichorionic twins vs. singletons  $P < 0.0001$ , median difference = 0.11 (95% confidence intervals (CI) = 0.085–0.14); monozygotic vs. singletons  $P = 0.02$ , median difference = 0.08 (95% CI = 0.16–0.005)). However, there was no significant difference

**Table 1** Demographic and screening characteristics of women in the study population. Numbers in parentheses represent ranges or percentages

	Dichorionic twins n = 316	Monochorionic twins n = 35	P-value
Age at screening, years, median (range)	31.7 (18–46)	29.6 (19–40)	0.06
White, n (%)	234 (74.1)	27 (77.2)	
Black, n (%)	61 (19.3)	3 (8.6)	0.10
Other, n (%)	21 (6.6)	5 (14.3)	
Nulliparous, n (%)	107 (33.9)	11 (31.4)	0.92
Cigarette smoker, n (%)	43 (13.6)	6 (17.1)	0.61
Body mass index, median (range)	23.9 (19.4–41.2)	25.4 (16.4–49.1)	0.11
Gestation, weeks, median (range)	23.1 (22.1–24.9)	23.3 (22.1–24.4)	0.64
Pulsatility index (PI), median (range)	0.90 (0.56–2.15)	0.95 (0.65–1.84)	0.42
PI above 95th centile, n (%)	16 (5.1)	2 (5.7)	0.70
Bilateral notches, n (%)	11 (3.5)	1 (2.9)	1

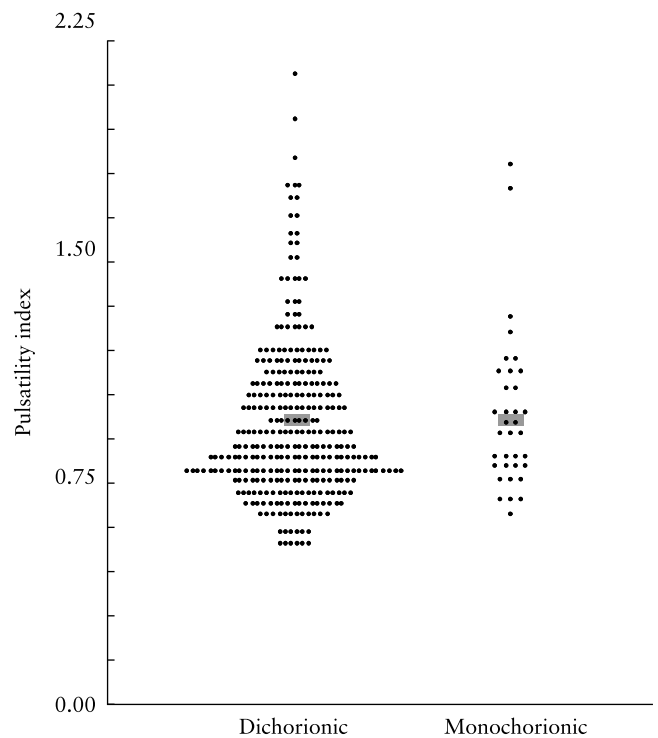
**Table 2** Outcomes in the study population (n = 351)

Outcome	All twins n = 351		Dichorionic n = 316		Monochorionic n = 35		P-value
	n	%	n	%	n	%	
Pre-eclampsia	21	6.0	19	6.0	2	5.7	
Fetal growth restriction (both twins < 5th centile)	31	8.8	28	8.9	3	8.6	1
Fetal growth restriction (one twin < 5th centile)	83	23.6	79	25.0	4	11.4	0.11
Fetal growth restriction (both twins < 3rd centile)	22	6.3	21	6.6	1	2.9	0.71
Fetal growth restriction (one twin < 3rd centile)	63	17.9	59	18.7	4	11.4	0.41
Pregnancy affected by abruption	3	0.9	3	0.9	0	0	—
Pregnancy affected by stillbirth	6	1.7	5	1.6	1	2.9	0.47
Preterm delivery at ≤ 32 completed weeks	43	12.3	36	11.4	7	20.0	0.17

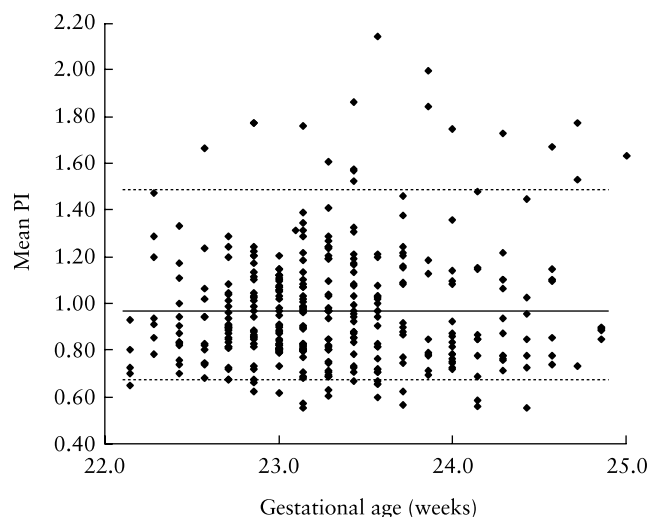
in mean PI between the dichorionic and monochorionic groups ( $P = 0.42$ , median difference 0.03 (95% CI = -0.04–0.105); Figure 1). Similarly, the incidence of bilateral uterine artery notches was significantly lower in twins as compared to singletons (3.4% vs. 9.3%,  $P = 0.003$ ) but there was no significant difference between dichorionic and monochorionic twins (3.5% vs. 2.9%,  $P = 1$ ).

As there were no significant differences between dichorionic and monochorionic twins in the demographic characteristics, screening indices, outcome measures or distribution of mean PI, subsequent analysis was carried out on the two groups of twins as a whole. The uterine artery mean PI did not change significantly with gestation ( $r = 0.0081$ ,  $P = 0.088$ , Figure 2). The median mean PI was 0.91 and the 95th centile was 1.5 (Figure 3). In 3.4% of cases there were early diastolic notches in the waveform of both uterine arteries (Table 1).

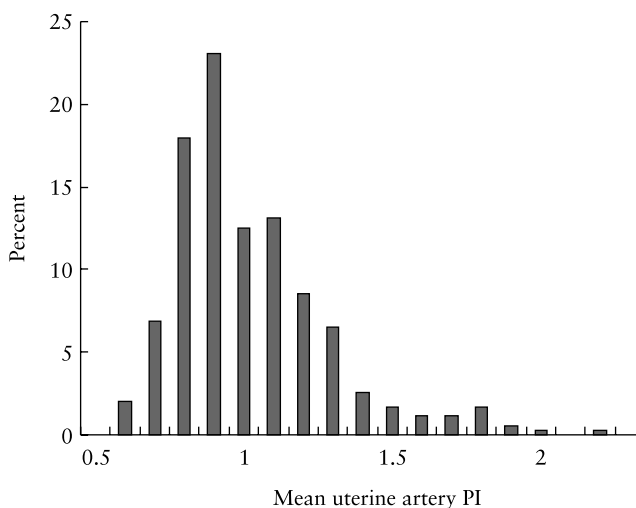
Screening characteristics for the outcomes of interest are shown in Table 3 for PI above the 95th centile, irrespective of the presence or absence of uterine artery notches, and in Table 4 for bilateral notches irrespective of mean PI. There were 12 women with bilateral notches and in seven of these the mean PI was above the 95th centile. In the seven cases with both high mean PI and bilateral notches there was a particularly high incidence of complications, with six women (86%) suffering one or more adverse outcomes (Table 5). In contrast, in the five cases with bilateral notches but normal PI there were two pregnancies where one fetus was smaller



**Figure 1** Spread plot of uterine artery mean pulsatility index (PI) in dichorionic and monochorionic twin pregnancies. The median is represented by the shaded line.



**Figure 2** Scattergram showing mean pulsatility index (PI) against gestational age at screening with the solid line showing the mean value and the dashed lines the 5th and 95th percentiles.



**Figure 3** Histogram of the distribution of uterine artery mean pulsatility index (PI) in the study population.

**Table 3** Screening characteristics for mean pulsatility index above the 95th centile (1.5) which was found in 18 of the 351 (5.1%) pregnancies

	n	Sensitivity	Specificity	PPV	NPV	LR (+ ve)	95% CI
Pre-eclampsia	21	7/14 (33.3%)	96.7%	38.9%	95.8%	10.00	4.24–21.88
FGR (both twins) < 5th centile	31	3/31 (9.7%)	95.3%	16.7%	91.6%	2.06	0.65–6.03
FGR (one twin) < 5th centile	83	5/83 (6.0%)	95.1%	27.8%	76.6%	1.24	0.46–3.21
FGR (both twins) < 3rd centile	22	3/22 (13.6%)	95.4%	16.7%	94.3%	2.99	0.95–8.43
FGR (one twin) < 3rd centile	63	4/63 (6.3%)	95.1%	22.2%	82.3%	1.31	0.45–3.58
Abruption	3	2/3 (66.6%)	95.4%	11.1%	99.7%	14.50	4.20–28.27
Intrauterine death	6	2/6 (33.3%)	95.4%	11.1%	98.8%	7.19	1.94–18.47
Preterm delivery at ≤ 32 weeks	43	8/43 (18.6%)	96.8%	44.4%	89.5%	5.73	2.41–13.17

FGR, fetal growth restriction; PPV, positive predictive value; NPV, negative predictive value; LR (+ ve), likelihood ratio for a positive test; CI, confidence interval.

**Table 4** Screening characteristics for bilateral notches, which were found in 12 of the 351 (3.4%) of pregnancies

	n	Sensitivity	Specificity	PPV	NPV	LR (+ ve)	95% CI
Pre-eclampsia	21	4/21 (19.0%)	97.6%	33.3%	95.0%	7.86	2.61–21.86
FGR (both twins) < 5th centile	31	1/31 (3.2%)	96.6%	8.3%	91.2%	0.94	0.16–5.18
FGR (one twin) < 5th centile	83	5/83 (6.0%)	97.4%	41.7%	77.0%	2.31	0.79–6.67
FGR (both twins) < 3rd centile	22	1/22 (4.5%)	96.7%	8.3%	93.8%	1.36	0.23–7.26
FGR (one twin) < 3rd centile	63	5/63 (7.9%)	97.6%	41.7%	82.9%	3.27	1.12–9.36
Abruption	3	1/3 (33.3%)	96.8%	8.3%	99.4%	10.55	1.83–33.38
Intrauterine death	6	0/6 (0%)	96.5%	0%	98.2%	—	—
Preterm delivery at ≤ 32 weeks	43	5/43 (11.6%)	97.7%	41.7%	8.8%	5.12	1.76–14.42

FGR, fetal growth restriction; PPV, positive predictive value; NPV, negative predictive value; LR (+ ve), likelihood ratio for a positive test; CI, confidence interval.

**Table 5** Outcomes in the seven cases with mean PI above the 95th centile and bilateral notches at 22–24 weeks

Case	Gestational age at delivery (weeks)	Pre-eclampsia	Abruption	FGR < 3rd (one twin)	FGR < 3rd (both twins)	Any complication?
1	28 + 6	Yes	Yes	Yes		Yes
2	33 + 5	Yes			Yes	Yes
3	33 + 6	Yes		Yes		Yes
4	29 + 6	Yes				Yes
5	34 + 1			Yes		Yes
6	30 + 3					Yes
7	36 + 2					No

than the 3rd centile, but no other adverse outcomes. Therefore, defining an abnormal result as mean PI above the 95th centile or bilateral notches did not increase the detection of any of these other adverse outcomes, while increasing the screen-positive rate from 5.1% to 6.6%.

## DISCUSSION

The finding of this study that in twin pregnancies PI in the uterine arteries is lower than in singleton pregnancies, is consistent with that of previous reports<sup>15,16</sup>. Furthermore, there was no significant difference in uterine artery mean PI or incidence of bilateral notches between dichorionic and monochorionic twin pregnancies. This is not surprising, because there was no significant difference in adverse outcomes between dichorionic and monochorionic twins. For pre-eclampsia, this is in keeping with a previous report by Savvidou *et al.* where chorionicity was also determined prospectively<sup>17</sup>. In contrast, previous studies reported a higher incidence of FGR in monochorionic twins<sup>18</sup> and the absence of this finding in our study is likely to be the consequence of excluding pregnancies with features of twin-to-twin transfusion syndrome. Similarly, the absence of significant differences in the incidence of early preterm delivery may also be due to the exclusion of pregnancies with this complication.

The study has demonstrated that a large proportion of twin pregnancies destined to suffer with adverse pregnancy outcomes may be predicted by a simple, one-stage screening test at 22–24 weeks of gestation. Overall, the predictive ability of the test was not as high as for singleton pregnancies. Thus, for pre-eclampsia we have previously reported a sensitivity of 41% for a 5.1% screen-positive rate, using the same methodology and the 95th percentile for singletons (1.63) as a cut-off<sup>11</sup>. This compares with a sensitivity of 33% in the current study for the same screen-positive rate (at the lower 95th centile of 1.5). The incidence of pre-eclampsia in twin pregnancies is higher than in singletons and consequently the positive predictive value for this condition in twins (39%) is higher than in singletons (12%). Women with high mean PI and bilateral notches constituted a particularly high risk group, and this is in keeping with previous reports from singleton pregnancies<sup>19</sup>. In the only previous study of Doppler screening in twins for pre-eclampsia, the incidence of this complication was 25% and the sensitivity for the prediction, using mean RI, was 37.5% for a specificity of 66%, a positive predictive value of 13.6% and a negative predictive value of 88%<sup>15</sup>. However, the screen-positive rate was not reported and it is therefore not possible to make direct comparison with our study. The sensitivity in the current study is broadly similar (33%), but with a higher specificity (97%), positive predictive value (39%) and negative predictive value (96%).

The sensitivity for FGR below the 5th centile is also less than that reported in singletons (about 10% and 6% for FGR of both or one twin, respectively, compared with 19% for singletons). The incidence of FGR was higher than that in singletons: in total 21% of infants had birth weights below the 5th centile of the reference range for singletons, and 15%

of them were below the 3rd centile. Despite this high incidence, the likelihood ratios for developing these complications were not significantly different from unity. There was, however, a tendency for improved sensitivity with more severe forms of FGR.

Increased uterine artery mean PI also identified the majority of pregnancies complicated by placental abruption and about one-third of those suffering an intrauterine fetal death. The test also identified about one-fifth of pregnancies delivering before 32 completed weeks of gestation, but this was mainly because of pregnancies requiring iatrogenic preterm delivery because of pre-eclampsia or FGR.

The results of this multicenter screening study show that Doppler assessment of the uterine arteries at 23 weeks identifies a considerable proportion of twin pregnancies destined to develop adverse outcomes related to uteroplacental insufficiency. The study confirms the finding of work on singleton pregnancies that, for the same screen-positive rate, the sensitivity of mean PI for pre-eclampsia is higher than that with bilateral notches, and that women with high mean PI and bilateral notches constitute a particularly high risk group. Prediction of adverse outcomes may aid in stratification of antenatal care by increasing surveillance in the screen-positive group. In the presence of increased mean PI, there is an approximately 10-fold increased risk of developing pre-eclampsia, a 14-fold increased risk of developing abruption and a seven-fold increased risk of suffering an intrauterine death.

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